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Levofloxacin vs. ciprofloxacin plus phenethicillin for the prevention of bacterial infections in patients with haematological malignancies

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ABSTRACT

An open-label randomised clinical trial was designed to compare the efficacy and tolerance of levofloxacin and ciprofloxacin plus phenethicillin for the prevention of bacterial infections in patients with high-risk neutropenia, and to monitor the emergence of antimicrobial resistance. Adult patients (n = 242) scheduled to receive intensive treatment for haematological malignancies were assigned randomly to receive oral prophylaxis with either levofloxacin 500 mg once-daily (n = 122), or ciprofloxacin 500 mg twice-daily plus phenethicillin 250 mg four-times-daily (n = 120). The primary endpoint was failure of prophylaxis, defined as the first occurrence of either the need to change the prophylactic regimen or the initiation of intravenous broad-spectrum antibiotics. This endpoint was observed in 89 (73.0%) of 122 levofloxacin recipients and in 85 (70.8%) of 120 ciprofloxacin plus phenethicillin recipients (RR 1.03, 95% CI 0.88–1.21, p 0.71). No differences were noted between the two groups with respect to secondary outcome measures, including time to endpoint, occurrence of fever, type and number of microbiologically documented infections, and administration of intravenous antibiotics. A questionnaire revealed that levofloxacin was tolerated significantly better than ciprofloxacin plus phenethicillin. Surveillance cultures indicated the emergence of viridans group (VG) streptococci resistant to levofloxacin in 17 (14%) of 122 levofloxacin recipients; in these cases, the prophylactic regimen was adjusted. No bacteraemia with VG streptococci occurred. It was concluded that levofloxacin and ciprofloxacin plus phenethicillin are equally effective in the prevention of bacterial infections in neutropenic patients, but that levofloxacin is tolerated better. Emergence of levofloxacin-resistant VG streptococci is of concern, but appears to be a manageable problem.

Keywords Infection, neutropenia, prophylaxis, quinolones, resistance, tolerance

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INTRODUCTION

Quinolones have been used extensively in the past two decades for the prevention of bacterial infections during neutropenia in cancer patients. It is evident that this approach reduces the incidence of Gram-negative bacteraemia significantly [1–3]. Unfortunately, this is counterbalanced by an increased incidence of infections with Gram-positive bacteria. In particular, viridans group (VG) streptococci and coagulase-negative staphylococci have emerged as a frequent cause of morbidity and mortality [4,5]. To overcome this problem, quinolone prophylaxis has been combined with other antimicrobial agents, e.g., penicillin, macrolides and vancomycin, that are active against Gram-positive cocci [6–9].

An alternative approach could involve the use of new-generation quinolones, which are more potent against Gram-positive pathogens. Levofloxacin, as a representative of this group, has been reported to reduce the incidence of fever and other infection-related outcomes in neutropenic cancer patients, compared with a placebo [2,10,11], but important issues remain to be addressed. First, no data are available from controlled clinical trials that allow a direct

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comparison between the use of levofloxacin prophylaxis and the use of ciprofloxacin plus an antibiotic with anti-Gram-positive bacteria activity. Second, there have been some alarming reports concerning the emergence of levofloxacin-resistant Gram-positive microorganisms, in particular VG streptococci [12,13].

During the past few years, patients admitted to the haematology department of the VU University Medical Center, Amsterdam, The Netherlands have received ciprofloxacin plus phenethicillin for the prevention of bacterial infections during neutropenia as the standard of care. When levofloxacin became available in The Netherlands, the randomised clinical trial described in this study was conducted to compare levofloxacin with ciprofloxacin plus phenethicillin with respect to their efficacy as antibacterial prophylaxis for neutropenic patients. In addition, the trial was designed to investigate the tolerance of these compounds and to closely monitor emerging antimicrobial resistance.

PATIENTS AND METHODS

Patients

Consecutive adult patients with a haematological malignancy who were hospitalised at the haematology department of the VU University Medical Center for high-dose combination chemotherapy, with or without autologous or allogeneic haematopoietic stem-cell transplantation, were eligible for this study. An anticipated granulocytopenic period (granulocytes $<0.5 \times 10^9$/L) of ≥10 days was required. Patients were enrolled only once. Exclusion criteria were active infection or antibacterial therapy at entry, a history of hypersensitivity to fluoroquinolones, a creatinine clearance of <15 mL/min, or elevation of transaminases to greater than three-fold the normal upper limit. The protocol was approved by the institutional scientific and ethical committees, and all participants provided written informed consent.

Randomisation and prophylactic regimen

The study was a prospective, single-centre, open-label, randomised clinical trial. Patients were assigned randomly by consecutively drawn, sealed envelopes to receive either levofloxacin 500-mg tablets once-daily or ciprofloxacin 500-mg tablets twice-daily, plus, from day 7 after the start of chemotherapy, phenethicillin 250-mg tablets four-times-daily. Prophylaxis was begun on the first day of chemotherapy and was continued until recovery to a granulocyte count of $>0.5 \times 10^9$/L. Phenethicillin was initiated on day 7 because, from that time on, oropharyngeal mucositis was to be expected, and this has been identified as an independent risk-factor for infections with streptococci [4]. Compliance was monitored by counting tablets. In addition to the study medication, all patients received fluconazole 50 mg once-daily and 2 mg nasal amphotericin B spray three-times-daily. A central venous catheter was inserted before the start of chemotherapy.

Clinical and microbiological evaluation of subjects

Randomised patients were examined daily for clinical signs of infection. Surveillance cultures for identification of colonising bacteria and yeasts were taken from throat and anus before the first dose of the study drugs and once-weekly thereafter. If appropriate, the prophylactic regimen was adjusted according to the resistance patterns of the microorganisms identified.

If the axillary temperature increased to >38.5°C, or if other signs or symptoms of an infection occurred without fever, clinical evaluation took place according to a local protocol, including a complete physical examination, a chest X-ray, and appropriate samples for microbiological cultures. At least two separate blood samples were obtained for culture, from both the central venous catheter and from a peripheral vein. Subsequently, empirical antibiotic therapy was initiated, consisting of intravenous imipenem–cilastatin 500 mg four-times-daily. If the fever did not resolve in ≤96 h, patients received antifungal therapy. In case of initiation of broad-spectrum antibacterial therapy, levofloxacin or ciprofloxacin were continued, but phenethicillin was discontinued.

Pathogenic microorganisms, isolated either from surveillance cultures or from cultures obtained from patients with presumed infection, were identified to the species level by standard microbiological techniques. MICs of levofloxacin and ciprofloxacin for staphylococci, streptococci and Gram-negative bacilli were determined by Etests (AB Biodisk, Solna, Sweden). Susceptibility of streptococci to phenethicillin was determined by disk-diffusion tests and was reported as susceptible, intermediately-resistant or resistant. Breakpoints were defined according to CLSI standards.

Tolerance of the study medication and toxicity

Patients were asked to complete a questionnaire, which recorded a 'tolerance score' for the study medication on a daily basis. Tolerance of the study drug was classified as 'not able to take the study drug', 'difficult intake', 'minor problems on intake', or 'intake without any problem'. Any adverse event that was possibly or probably related to the study medication was recorded. Routine clinical chemistry tests were performed weekly, and any deterioration in liver enzymes, bilirubin or kidney function was recorded. All adverse events were classified using the Common Terminology Criteria for Adverse Events v.3.0 (CTCAE; National Cancer Institute, Bethesda, MD, USA). Following an adverse event, study medication was either continued or discontinued, according to the judgement of the responsible physician.

Outcome

The primary outcome measure of the study was success or failure of the prophylactic regimen. Failure of prophylaxis was a composite endpoint, defined as the need to change the prophylactic regimen for any reason, or the initiation of broad-spectrum antibacterial therapy, whichever event occurred first. The primary endpoint was chosen to reflect the effects of the prophylactic regimens on the most relevant clinical events.

Furthermore, the study was designed to include patient follow-up beyond this first event, and data were analysed on an intention-to-treat basis. Secondary outcome measures were the time to primary endpoint, the occurrence of fever, the type and number of documented infections, the use of antimicrobial agents, and the tolerance of the study drug. Moreover, the study design provided close monitoring of the acquisition of antimicrobial resistance by the pathogens isolated.

Statistical evaluation

It was estimated from previous studies in the same ward that *c.* 30% of patients survive the neutropenic episode without requiring change of prophylaxis or initiation of broad-spectrum antibiotics. Thus, according to the definitions used in the present study, 70% of patients were expected to experience failure of prophylaxis. Sample size was calculated to detect a 25% reduction (from 70% to 52%) in failure of prophylaxis. To detect such a difference with a significance level (α) of 0.05 (two-tailed) and a statistical power of 80%, 120 patients per arm were required. Differences between groups in categorical variables were analysed with the chi-square test. In case of variables with an ordering or grading scale, the chi-square test for trend was used. The relative differences between the groups were also expressed as relative risks (RRs) with 95% CIs. The Mann–Whitney non-parametric *U*-test was used for comparison of means. Differences in survival without failure of prophylaxis were assessed by the log-rank test, and Kaplan–Meier curves were plotted for each study group.

RESULTS

Between January 2002 and July 2005, 245 patients were enrolled in the study. Three patients were excluded from analysis. One patient withdrew informed consent, another patient was erroneously enrolled twice, and one patient died on the day of randomisation because of disease progression. Of the 242 evaluable patients, 122 were assigned to receive levofloxacin and 120 to receive ciprofloxacin and phenethicillin. Basic patient characteristics of the two treatment groups are listed in Table 1. No significant differences were found in gender, age, type and remission status of the haematological disease and treatment variables, including stem-cell transplantation procedures. However, the neutropenic episode was significantly longer in the ciprofloxacin–phenethicillin group (mean difference to a granulocyte count of $>0.5 \times 10^9$/L = 1.4 days, p 0.044; mean difference to granulocyte count $>0.1 \times 10^9$/L = 1.6 days, p 0.017). Patients receiving levofloxacin remained in hospital for a mean of 25.5 days, compared with 28.1 days for patients receiving ciprofloxacin–phenethicillin, but this was not statistically significant (mean difference 2.6 days, p 0.13).

Table 1. Characteristics of patients included in the study

	Levofloxacin		Ciprofloxacin	
	n	%	*n*	%
Total patients	122	50.4	120	49.6
Age, median, years (range)	55 (18–71)		54 (19–71)	
Gender				
Male	76	62.3	79	65.8
Female	46	37.7	41	34.2
Diagnosis				
ALL	10	8.2	10	8.3
AML	19	15.6	28	23.3
Multiple myeloma	46	37.7	39	32.5
Lymphoma	35	28.7	34	28.4
Myelodysplasia	4	3.3	3	2.5
Other	8	6.5	6	5.0
Stem-cell transplantation	86	70.5	78	65.0
Autologous stem cells	74	86.0	65	83.3
Allogeneic stem cells	12	14.0	13	16.7

All differences not significant.
ALL, acute lymphocytic leukaemia; AML, acute myeloid leukaemia.

Failure of prophylaxis and febrile episodes

The primary endpoint 'failure of prophylaxis' was observed in 89 (73.0%) of 122 patients receiving levofloxacin, compared with 85 (70.8%) of 120 patients receiving ciprofloxacin–phenethicillin (RR 1.03, 95% CI 0.88–1.21, p 0.71). The distribution of events responsible for failure of prophylaxis, change of the prophylactic regimen and initiation of intravenous antibiotics were similar in the two groups. The time to failure of prophylaxis, and Kaplan–Meier estimates of the proportion of patients surviving without failure of prophylaxis, showed no clear advantage for either prophylactic regimen.

In the intention-to-treat analysis, 28 (23.0%) of 122 patients in the levofloxacin group needed adjustment of the prophylactic regimen during the study period, compared with 39 (32.5%) of 120 patients in the ciprofloxacin–phenethicillin group (RR 0.71, 95% CI 0.47–1.07, p 0.07). The main reason for change of prophylaxis in the levofloxacin group was decreased susceptibility or resistance of bacterial isolates, as indicated by surveillance culture data. Intolerance of the study medication was the most common reason for change of the prophylactic regimen in patients receiving ciprofloxacin–phenethicillin. This event occurred significantly less frequently in levofloxacin recipients (RR 0.11, 95% CI 0.03–0.46, p 0.0002).

The occurrence and duration of fever, and the number of patients receiving broad-spectrum intravenous antibiotics, were similar in both groups. Furthermore, there were no significant differences in either type or number of antibacterial and antifungal antibiotics administered. The number of days (mean ± SD) for which patients received intravenous antibiotics was 9.2 ± 7.1 in the levofloxacin group compared with 10.9 ± 7.4 in the ciprofloxacin–phenethicillin group. The difference of 1.7 days in favour of the levofloxacin group almost reached statistical significance (p 0.051).

Infections

The number of microbiologically documented infections was similar in both groups, with 21 (17.2%) of such infections observed in levofloxacin recipients and 22 (18.3%) in ciprofloxacin–phenethicillin recipients (RR 0.94, 95% CI 0.55–1.62, p 0.82). Most patients with a microbiologically documented infection had bacteraemia, with a predominance of single Gram-positive microorganisms. Bacteraemia with Gram-negative microorganisms was a rare event and occurred in only two patients receiving levofloxacin (one patient with a single Gram-negative organism and one with polymicrobial bacteraemia), and was not observed among patients receiving ciprofloxacin-–phenethicillin. Clinically documented infections encompassed predominantly pulmonary infiltrates on the chest X-ray, and mouth or throat ulcerations. These infections were observed in 12 (9.8%) levofloxacin recipients and in 18 (15.0%) ciprofloxacin–phenethicillin recipients (RR 0.66, 95% CI 0.33–1.30, p 0.22). Fever of unknown origin occurred in 40 (32.8%) levofloxacin recipients and in 29 (24.2%) ciprofloxacin–phenethicillin recipients (RR 1.36, 95% CI 0.90–2.04, p 0.13).

Microbiological evaluations

Throat surveillance cultures (levofloxacin, $n = 448$; ciprofloxacin–phenethicillin, $n = 485$) yielded predominantly VG streptococci (Table 2). From day 1 to day 4, VG streptococci were found in 111 (91%) of 122 patients in the levofloxacin group, compared with 108 (90%) of 120 patients in the ciprofloxacin–phenethicillin group. During the subsequent study period, the number of patients with throat surveillance cultures that yielded VG streptococci decreased in both groups. However, the colonisation rate of VG streptococci was reduced faster and to a larger extent over time in the levofloxacin group compared with the ciprofloxacin–phenethicillin group (chi-square for trend, p <0.0001). From day 1 to day 4, 107 (96%) of 111 VG streptococcal isolates from levofloxacin recipients were susceptible to levofloxacin, two (2%) were resistant and two (2%) were intermediately-susceptible. In contrast, only 25 (23%) of 108 VG streptococcal isolates from ciprofloxacin–phenethicillin recipients were susceptible to ciprofloxacin, 12 (11%) were resistant and 71 (66%) were intermediately-susceptible. VG streptococci resistant to phenethicillin were not isolated from patients receiving ciprofloxacin–phenethicillin prophylaxis, although isolates from 30 patients had intermediate susceptibility. Anal surveillance cultures (levofloxacin, $n = 469$; ciprofloxacin–phenethicillin, $n = 503$) yielded predominantly *Escherichia coli* and other Enterobacteriaceae. Eradication of these microorganisms was highly efficient with both prophylactic regimens. At baseline, two patients in each group had

Table 2. Pathogens isolated and their resistance patterns

	No. of patients with isolate			
	Levofloxacin		Ciprofloxacin	
	Total	Resistant	Total	Resistant
Surveillance cultures				
Gram-positive microorganisms				
VG streptococci, at baseline	111	2	108	12
VG streptococci, from day 4	67	17	101	51
β-Haemolytic streptococci, at baseline	12	0	16	0
β-Haemolytic streptococci, from day 4	2	0	1	0
Staphylococcus aureus, at baseline	7	0	6	0
S. aureus, from day 4	0	0	1	0
Gram-negative microorganisms				
Escherichia coli, at baseline	81	2	79	2
E. coli, from day 4	12	3	7	4
Other Enterobacteriaceae, at baseline	40	0	42	0
Other Enterobacteriaceae, from day 4	5	0	3	0
Pseudomonas aeruginosa	1	0	2	0
Bacterial isolates				
Blood				
Coagulase-negative staphylococci	18	18	21	21
Enterococci	5	5	6	6
VG streptococci	0	0	2	2
S. aureus	0	0	1	1
Stenotrophomonas maltophilia	1	1	0	0
Serratia marcescens	1	0	0	0
Sputum or bronchoalveolar lavage fluid				
Sten. maltophilia	2	1	0	0
Legionella pneumophila	0	0	1	1
Other sites				
Enterococci	3	2	2	1

VG, viridans group.

quinolone-resistant *E. coli*. Acquired resistance in *E. coli* during the study period was observed for one patient receiving levofloxacin, and for two patients receiving ciprofloxacin–phenethicillin. Most bacterial isolates from blood cultures and from cultures of other sites were resistant to levofloxacin and ciprofloxacin (Table 2). The number and type of bacteria isolated were similar in both groups, with coagulase-negative staphylococci and enterococci identified most frequently.

Tolerance of study drug and adverse events

The questionnaire concerning daily tolerance of the study medication was completed by 100 patients receiving levofloxacin (response rate 82%) and by 79 patients receiving ciprofloxacin–phenethicillin (response rate 66%). From day 4, the mean tolerance score per day was significantly lower for ciprofloxacin–phenethicillin recipients than for patients receiving levofloxacin ($p < 0.05$), indicating that patients considered the intake of levofloxacin less problematic than that of ciprofloxacin–phenethicillin.

Biochemistry values, expressed as maximum CTCAE toxicity grade of transaminases, creatinine and albumin levels, were similar for the two groups, both at baseline and during the study period. In addition, adverse events were documented at the same frequency in the two treatment groups. Skin rash was observed most frequently, occurring in 16 (13.1%) levofloxacin recipients and 15 (12.5%) ciprofloxacin–phenethicillin recipients (RR 1.05, 95% CI 0.54–2.03, p 0.89).

Mortality

The overall mortality rate was 2.5% (six of 242 patients). Two patients in the levofloxacin group died, one from sinusoidal obstruction syndrome of the liver, and the other from respiratory failure caused by a pulmonary infection, with no causative microorganism identified. Four patients died in the ciprofloxacin–phenethicillin group, one from a probable infection with *Aspergillus fumigatus*, a second from cardiac arrest, and two from respiratory failure. Of the last two patients, the alveolar lavage fluid from one patient yielded flavobacteria and *Candida albicans*, while cultures remained negative for the other patient.

DISCUSSION

The results of this randomised controlled clinical trial demonstrate that levofloxacin and ciprofloxacin plus phenethicillin are equally successful as antibacterial prophylaxis for neutropenic patients with haematological malignancies. Failure of prophylaxis, as the primary outcome measure, was observed at the same frequency in the two treatment groups, as were its composites: the initiation of broad-spectrum antibacterial antibiotics, and the need for change of the prophylactic regimen. Other infection-related outcomes, e.g., the time to failure of prophylaxis, occurrence of fever, the number of patients with a microbiologically documented infection, and the number of patients who received broad-spectrum intravenous antibiotics, did not favour either of the prophylactic strategies. However, patients receiving ciprofloxacin–phenethicillin had a discrete, but significantly longer, duration of neutropenia of *c.* 1.6 days. This finding probably accounts for the trend towards a longer duration of hospital stay for these patients, and may be an explanation for the (almost significant) higher number of days for which patients in the ciprofloxacin–phenethicillin group needed intravenous antibiotics. It is well-known that prolonged administration of β-lactam antibiotics may induce neutropenia, probably because of a direct toxic effect on the bone marrow or an immune-mediated effect [14,15]. Considering the fact that duration of neutropenia has been identified as an independent risk-factor for the occurrence and severity of infections, and as a critical factor in a successful outcome, this finding may be of clinical importance [16,17].

It was assumed that patients receiving one tablet of levofloxacin per day would tolerate the study medication better than patients receiving two tablets of ciprofloxacin plus four tablets of phenethicillin. The results of the questionnaire confirmed this supposition. From day 4, the mean tolerance score for levofloxacin was significantly higher than the score for ciprofloxacin–phenethicillin. In line with these results, a change of prophylaxis because of intolerance of the study drugs was necessary for significantly more patients receiving ciprofloxacin–phenethicillin than for those receiving levofloxacin. Since these patients are commonly suffering from discomforting nausea and mucositis, a better tolerance of

prophylactic medication is important and may improve therapy compliance. However, the results of the questionnaire need to be interpreted with caution. The response rate was 82% in the levofloxacin group and 66% in the ciprofloxacin–phenethicillin group, which may indicate selection bias. Patients were sometimes disappointed not to have been assigned to receive levofloxacin, and other patients became very ill during the study period. It is possible that these patients, in particular, were less motivated or less able to complete and return the questionnaire.

The prophylactic administration of both ciprofloxacin–phenethicillin and levofloxacin resulted in good control over Gram-negative bacteria, and only two patients, both receiving levofloxacin, developed Gram-negative bacteraemia. The efficacy of quinolone prophylaxis in reducing Gram-negative infections has been well-documented, although the emergence of quinolone-resistant bacteria, particularly *E. coli*, has been reported [18,19]. Moreover, prophylaxis with the older-generation quinolones, e.g., ciprofloxacin, has been associated with an increase in the number of Gram-positive infections. Levofloxacin and other newer quinolones have enhanced activity against Gram-positive microorganisms, and may potentially overcome this problem. However, early reports concerning levofloxacin administered as antibacterial prophylaxis suggest that its use may be associated with the selection of quinolone-resistant VG streptococci [12,13]. This is a major drawback, as these microorganisms have been reported to be responsible for up to 39% of cases of bacteraemia in neutropenic patients, and may result in serious complications, including endocarditis, adult respiratory distress syndrome, shock and even death [4,13,20]. In the present study, surveillance cultures yielded levofloxacin-resistant VG streptococci from 17 (14%) of 122 levofloxacin recipients. In these patients the prophylactic regimen was adjusted, in most instances by the addition of penicillin. This proved to be a valuable approach, as no bacteraemia with VG streptococci occurred in the levofloxacin group. However, in agreement with data published previously, the bacteria isolated most frequently from patients with a bloodstream infection were coagulase-negative staphylococci and enterococci [20,21]. As expected, these bacteria were invariably resistant to levofloxacin and ciprofloxacin. This finding should be taken into account in the choice of empirical antibiotic therapy, and underscores the importance of meticulous care of central venous access devices.

In conclusion, levofloxacin was as efficacious as ciprofloxacin plus phenethicillin for the prevention of bacterial infections in neutropenic patients with cancer. However, levofloxacin is better-tolerated, which may benefit compliance with therapy. Resistance in VG streptococci does occur, but this problem appears to be manageable if resistance patterns are monitored closely. The present study does not answer the question as to which patients with neutropenia benefit most from the prophylactic administration of levofloxacin and other quinolones, and nor does it support the unlimited or uncontrolled use of these agents. As outlined in the guidelines published by the Infectious Diseases Society of America [22], routine quinolone prophylaxis for all neutropenic patients is not recommended. Based on the estimated infection risk for their own category of neutropenic patients, and with careful consideration of local antimicrobial resistance patterns, physicians should weigh the benefits of quinolone prophylaxis against the potential dangers of this approach.

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